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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/164,862	10/01/1998	PAUL A. PRICE	023070-08672	7170

22798 7590 06/23/2005

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/164,862	PRICE ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18,38,39,47,49 and 56-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-18,38,39,47,49 and 56-67* is/are rejected.

7)☐ Claim(s) *49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed January 12, 2005 is acknowledged and has been entered. Previously pending claims 38 and 47 have been amended and claims 63-67 were added. Applicant's submission filed March 25, 2005 is acknowledged and has been entered. Previously pending claim 47 has been amended, claims 50-51, 54-55 have been canceled. Claims 1-18, 38-39, 47, 49, 56-67 are currently pending and under prosecution. Action on the RCE follows.

It is noted that Applicant states that the Office Action mailed on 5/24/04 incorrectly showed claim 47 not pending and asks for clarification. A review of the action mailed revealed that Examiner made an inadvertent typographical error on the Office Action Summary that reflected the claims shown to be pending in paragraph 1 of the Office Action. However, it is clear that despite this typographical error, claim 47 was indeed examined. Applicant is referred to the rejection of claim 47 recited on page 5 of the action mailed 5/24/04. Examiner apologizes for any inconvenience.

It is further noted that Applicant points out an additional inadvertent typographical error wherein Examiner refers to an Office Action mailed October 15, 2003, wherein in fact the action was mailed on April 15, 2003. Examiner appreciates Applicant pointing out this error and confirms that the action referred to was in fact mailed April 15, 2003.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3, Claims 1-18, 63, 65, 67 are rejected under 35 USC 112, first paragraph because the specification, while enabling for a method of estimating survival expectancy of a cancer patient comprising measuring the level of YKL-40 in a cancer patient sample and comparing said patient sample YKL-40 level to the YKL-40 level found in normal control from the same sample type from normal healthy controls wherein a patient sample YKL-40 level greater than the 95th percentile for normal control YKL-40 levels is an indicator of a reduced survival expectancy, does not reasonably provide enablement for a method of estimating survival expectancy of a cancer patient comprising measuring the level of YKL-40 in a cancer patient sample and comparing said patient sample YKL-40 level to the YKL-40 level found in normal controls wherein a sample YKL-40 level in excess of YKL-40 levels in the same sample from said normal healthy humans is an indicator of a reduced survival expectancy compared to patients with normal YKL-40 level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method for estimating survival expectancy of a cancer patient comprising obtaining a biological sample comprising YKL-40 from a cancer patient and comparing the level to the YKL-40 level found in the same sample from normal healthy humans wherein a sample YKL-40 level in excess of YKL-40 levels in the same sample from a normal healthy humans

indicates a reduced survival expectancy compared to patients with normal YKL-40 level. This means any YKL-40 level in excess of YKL-40 levels from normal control.

The specification teaches in Table 1, p. 45 that YKL-40 levels in normal healthy humans ranges from 60-385 ug/L for women and 57-1015 ug/L in men. The specification further teaches that three healthy women, all of whom were free of any disease known to cause an elevation in serum YKL-40 had elevated levels of YKL-40 and that those levels were well above the 247 ug/L, the 95% level of controls. The specification further teaches that that serum levels of YKL-40 were measured in a clinical group of 60 breast cancer patients (p. 45, lines 10-19), 47 of which entered the study at the time that breast cancer recurrence was first suspected, 6 of whom did not have breast cancer recurrence, 6 had locally advanced disease or distant metastasis at the time of initial breast cancer diagnosis and 7 entered the study after recurrence (p. 26, lines 25-31). Data indicated that a serum YKL-40 level elevated above the 95% level of 120 normal women, correlates to decreased survival in patients with breast cancer (pgs 46-47).

One cannot extrapolate the teaching of the specification to the enablement of the claims because Johansen et al (European J. Of Cancer, Vol 31A, No. 9, pp. 1437-1442) of record, upon which the teachings of the specification appear to be based, reveals a comparison of YKL-40 in patients diagnosed with breast CA, wherein survival rates were less for patients with high serum YKL-40, that is at or above 95 percentile of controls, than those with normal serum YKL-40 at the time of entry into the study. In particular, the reference teaches the critical nature of the sensitivity and specificity of a potential biochemical marker and

that it may vary considerably according to different cut-off values. Given the data and the understanding of the critical nature of the sensitivity and specificity of YKL-40 as a biochemical marker, the authors selected a cut off for serum YKL-40 to 95 percentile of healthy age-matched women (p.1440). Further, as drawn to the cut-off point for YKL-40 for prediction of decreased survival. In particular, the specification teaches, as set forth above, that the data indicated that a serum YKL-40 level elevated above the 95% level of 120 normal women, correlates to decreased survival. In addition, in the Response submitted January 12, 2005, Applicant specifically points to numerous instances wherein "high" levels of YKL-40 were useful for correlating YKL-40 concentrations and survival expectancy, see pages 8-11 of the submission. In particular, in Jensen et al, Applicant points to "high" serum levels as prognostic of reduced survival for metastatic breast cancer patients. It is noted that the cut-off point used for this determination was the upper 90^{th} percentile of YKL-40 of normal controls (p. 4425, col 1). Applicant then points to Johansen et al, 2003, again drawn to breast cancer, wherein "high" serum levels are prognostic of reduced survival. It is noted that the cut-off point used for this determination was the 95 percentile of healthy females (see page 19, col 1). Applicant points to Dehn et al wherein "high" serum levels of YKL-40 are prognostic of reduced survival in ovarian cancer patients. It is noted that the cut-off point used for this determination was the 95 percentile of healthy females (see abstract). In particular, Applicant specifically pointed to the showing that OC patients with high plasma YKL-40 at the time of the first recurrence had significantly shorter survival than OC patients with normal or slightly elevated plasma YKL-40. It is noted that the claims as currently constituted are drawn only to a level "in excess" of normal

controls. Clearly, it would not be expected that survival expectancy of those patients with only slightly elevated plasma YKL-40/ patients with levels in excess of normal controls could be estimated with a reasonable expectation of success, based on the information in the references currently submitted. In particular, in each of the references cited, the indication of "high" levels of YKL-40 were based on levels greater than the upper 90 percentile of normal control levels of YKL-40 in serum. Although the specification does not provide support for a cut-off at the "upper 90^{th} percentile", it is clear that a cut-off point of the 95 percentile enables the claimed invention. It is also clear given the teachings in the specification, the art of record, and Applicant's arguments that this cut-off point is critical to the specificity and sensitivity of the claimed method. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed method would function as currently claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

4. Claims 47, 49, 56-62, 66 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of said assay "wherein said elevation is unrelated to known causes of YKL-40 elevation other than cancer" claimed in Claim 47 has no clear support in the specification and the claims as originally filed. Although the specification teaches that a significantly elevated blood or blood product level of YKL-40 typically indicates one or more of four possible pathological states and

suggests that having eliminated three of the four candidates recited, that follow-up for cancer detection is warranted (page 13, lines 5-25), although this provides support for assaying for the three cited disease types prior to diagnosis of cancer, this does not provide support for the newly added limitation. The subject matter claimed in claims 47, 49, 56-62, 66 broadens the scope of the invention as originally disclosed in the specification.

5. Claims 1-9, 11-18, 38-39, 63-65, 67 are rejected under 35 USC 112, first paragraph because the specification, while enabling for the claimed methods comprising obtaining a biological fluid sample for the measurement of YKL-40, does not reasonably provide enablement for said methods comprising obtaining a biological sample, assaying a primary tumor or a tissue affected by said cancer, assaying by immunohistochemical staining, assaying with tumor tissue cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to assay methods comprising obtaining a biological sample, assaying a primary tumor or a tissue affected by said cancer, assaying by immunohistochemical staining, assaying with tumor tissue cells. This means any tumor biological sample, any tissue affected by said cancer.

The specification teaches that the invention pertains to the discovery that YKL-40, a member of the chitinase protein family, provides a highly effective marker for the detection of a wide variety of diseases characterized by significant tissue remodeling (p. 11, lines 1-5) and that the sample can be a fluid or tumor tissue sample.

One cannot extrapolate the teaching of the specification to the scope of the claims because as previously set forth, the specification teaches that the source of YKL-40 which lead to elevated serum levels of protein in some colorectal cancer patients is not known but could arise from secretion by the tumor cells themselves, from secretion by inflammatory cells and from normal cells in areas of the colon adjacent to tumor (p. 55, lines 14-19). In addition, preliminary data investigating the expression of YKL-40 in colon cancer biopsies show that some cancers stain intensely for YKL-40 while others are completely negative (p. 55, lines 14-19). If elevated levels of serum YKL-40 do primarily reflect secretion from a subset of colorectal tumors, then the poor prognosis of patients with elevated serum YKL-40 suggests that YKL-40 expression may be associated with the ability of a tumor cell to invade normal tissues and to metastasize to distant sites (para bridging pages 55-56). Thus, given that YKL-40 is associated with significant tissue remodeling, given that significant tissue remodeling is associated with tissue invasion and metastasis, it is not clear if the metastasizing cells in fact are overexpressing or even secreting YKL-40 or whether the serum levels presented are associated with tissue remodeling processes unrelated to the specific cancer cells. Given the above, it is clear that although a subset of colon cancer tumors do overexpress YKL-40, the patients whose tumors will overexpress the marker cannot be predictably identified with a reasonable expectation of success. Further, the specification exemplifies the elevation of YKL-40 levels in prostate cancer wherein a pilot study was established to determine whether YKL-40 is elevated in prostate cancer with the ultimate goal of measuring serum YKL-40 in longitudinal studies of patients with prostate cancer in order to determine the precise

relationship between YKL-40 levels and survival, wherein 8 of 20 patients have serum YKL-40 levels above 247 ug/L, Based on these results, analysis will be undertaken of serum YKL-40 from past longitudinal studies of patients in which survival is known (p. 56, lines 16-27). Finally, the specification exemplifies the elevation of YKL-40 levels in small cell lung carcinoma patients wherein 40% of the patients tested had elevated serum YKL-40, greater than 208 ug/L, patients with high YKL-40, greater than 209 ug/L had a median survival rate significantly shorter than those with a normal serum YKL-40 (para bridging pages 57-58). Although the specification teaches that the sample tested may be primary tumor sample, given the information in the specification, given that the information in the prior art and currently submitted by the Applicant is all drawn to biological fluid sample, it appears that Applicant is aware of the unpredictability of using the instantly claimed assay methods with a reasonable expectation of success in any sample other than a biological fluid sample. For the reasons set forth above, it appears that undue experimentation would be required to practice the claimed invention as currently constituted.

New Grounds of Objection

Claim Objections

6. Claim 49 is objected to because of an apparent typographical error. Although the claim was properly amended, and ends with a period, it appears that an additional copy of the claim was inserted under the amended claim. Appropriate correction is required.

7. All other objections and rejections recited in the previous Final Rejection mailed May 24, 2005 are hereby withdrawn.

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Susan Ungar
Primary Patent Examiner
June 20, 2005